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(54) Potentiation of drug response by increasing serotonin availability

(57) The power of fluoxetine, venlafaxine and duloxetine to increase the availability or serotonin is augmented by administration in combination with WAY 100635.

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Description

Field of the invention

The present invention belongs to the fields of pharmacology, medicine and medicinal chemistry, and provides a method and compositions for increasing the availability of serotonin in the brain of patients to whom is administered fluoxetine, venlafaxine, milnacipran or duloxetine.

Background of the Invention

Over the past twenty years or more, the science of pharmacology has been particularly interested in the physiology of the neurons containing monoamines in the human brain. Discovery has followed discovery in the field and it has now been demonstrated that serotonin interacts with a great number of receptors in the brain and control or affect processes which regulate many bodily organs and functions. Serotonin has been found to be the key to a large number of processes which reveal themselves in both physiological and psychological functions.

Perhaps the most dramatic discovery in medicinal chemistry in the recent past is fluoxetine, a serotonin reuptake inhibitor, which is extremely effective in the treatment of depression. As a reuptake inhibitor, it increases the availability of serotonin in the synapse by reducing the uptake of serotonin by the serotonin uptake carrier. Disfunction of the serotonin neurons resulting from excessive uptake results in depression, as well as other pathologies of the central nervous system. Not only is fluoxetine spectacularly effective in depression, it is also effective in treating numerous other conditions. A next generation drug is duloxetine, which is a reuptake inhibitor of both serotonin and norepinephrine. It is now in advanced clinical trials in the treatment of both depression and urinary incontinence, and is a very effective drug. Venlafaxine is also reuptake inhibitor of both serotonin and norepinephrine.

The present invention provides a method for increasing the availability of serotonin, even compared to the usual increased availability caused by fluoxetine, venlafaxine, and duloxetine, by potentiating the action of those drugs. A related fundamental publication is F. Artigas, "5-HT and Antidepressants: New Views from Microdialysis Studies", Trends in Pharmacol. Sci. 14, 262 (1993).

Summary of the Invention

The invention provides a method for potentiating the action of a first component chosen from the group consisting of fluoxetine, venlafaxine, and duloxetine in increasing the availability of serotonin in the brain, comprising administering a first component in combination with a second component which is WAY 100635.

The invention also provides pharmaceutical compositions which comprise a first component in combination with the second component compound named above. Further, it provides methods of treating a pathological condition which is created by or is dependent upon decreased availability of serotonin, which comprise administering to a patient in need of such treatment an adjunctive therapy comprising a first component and one of the compounds named above.

Still further, the invention provides a preferred manner of carrying out the above method of adjunctive therapy wherein the second component is administered in a manner which provides a substantially constant blood level of the second component, which level is sufficient to provide a substantially constant degree of potentiation of the action of the first component. Compositions adapted for carrying out the preferred manner of the invention are also provided.

Description of the Preferred Embodiments

In this document, all temperatures are described in degrees Celsius, and all amounts, ratios of amounts and concentrations are described in weight units unless otherwise stated.

The compound

Fluoxetine, N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, is marketed in the hydrochloride salt form, and as the racemic mixture of its two enantiomers. U.S. Patent 4,314,081 is an early reference on the compound. Robertson et al., J. Med Chem. 31, 1412 (1988), taught the separation of the R and S enantiomers of fluoxetine and showed that their activity as serotonin uptake inhibitors is similar to each other. In this document, the word "fluoxetine" will be used to mean any acid addition salt or the free base, and to include the racemic mixture or either of the R and S enantiomers.

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Patent 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule.

Venlafaxine is known in the literature, and its method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake are taught by U.S. Patent 4,761,501. Venlafaxine is identified as compound A in that patent.

Duloxetine and fluoxetine, as well as verlataxine, are known to increase the availability of serotonin (5-HT) and the second component drugs potentiate that valuable property. WAY 100635 has the property of being an antagonist of the serotonin 1A receptor.

WAY 100635 (N-[2-[4-(2-methoxyphenyl)piperazin-1-yl]-N-(2-pyridyl)cyclohexanecarboxamide) was put in the literature by Cliffe et al., European Patent Publication 0512755, published November 11, 1992. A number of papers about the compound and its activity as a 5-HT1A antagonist were presented at the IUPHAR Satellite Meeting on Serotonin, July 30, 1994, Chicago, IL, and abstracts were published. See also Khawaja. J. Neurochem. 64, 2716-26 (1995); and Gozlan, Eur. J. Pharmacol. Mol. Pharm. Sec. 288, 173-86 (1995).

While all combinations of first component and second component compounds are useful and valuable, the combination of fluoxetine and WAY 100635 is particularly valued and is preferred.

It will be understood by the skilled reader that all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

Administration

The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here. Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs.

Fluoxetine: from about 1 to about 80 mg, once/day; preferred, from about 10 to about 40 mg once/day; more preferred, about 20 mg/day; preferred for bulimia and obsessive-compulsive disease, from about 20 to about 80 mg once/day;

Duloxetine: from about 1 to about 30 mg once/day; preferred, from about 5 to about 20 mg once/day;

Venlafaxine: from about 10 to about 150 mg once--thrice/day; preferred, from about 25 to about 125 mg thrice/day;

In more general terms, one would create a combination of the present invention by choosing a dosage of first component compound according to the spirit of the above guideline, and choosing a dosage of the second component compound in the general range of from about 1 to about 250 mg/dose. More preferred dosages would be from about 1 to about 100 mg/dose, and even more preferred dosages would be likely to be found in the range of from about 1 to about 50 mg/dose, ideally from about 1 to about 25 mg/dose.

The adjunctive therapy of the present invention is carried out by administering a first component together with the second component compound in any manner which provides effective levels of the two compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or may be administered separately.

However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. One of the drugs may be administered by one route, such as oral, and the other may be administered by the trans-dermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

It is particularly preferred, however, for the adjunctive combination to be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both a first component and the second component compound are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of both compounds, or may contain a fraction of the daily doses, such as one-third of the doses.

Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compound. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compound. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy

is being given.

The second component compound has short life in the body and, accordingly, provides only short periods of activity following each dose. In the context of the present invention, it is therefore preferred to administer the second component compound in a manner which supplies a substantially constant blood level of the second component in the body of the patient, at a sufficiently high level to provide a substantially constant degree of potentiation of the action of the first component.

It is not intended, of course, that the present invention or any method of human treatment can provide a truly constant blood level and degree of potentiation. Biological processes always vary and prevent precisely constant results. The term "substantially constant" is used herein to refer to administration resulting in blood levels and degrees of potentiation which are sufficiently constant as to provide continuous improved efficacy over a treatment day, compared to the efficacy of the first component compound alone. Another way to consider substantially constant potentiation is by comparing the availability of serotonin in the brain of the patient. By "Substantially constant" in such terms is meant a condition where the peak and the valley of availability differ by no more than about a factor of 2 over the course of a treatment day. Another way to consider "substantially constant" is a condition where the peak and valley differ by no more than about a factor of 1.5; or they differ by no more than a range of from about 1.5 no about 3.

Such administration of the second component may be provided by means known to pharmaceutical scientists. For example, the total daily dosage may be formulated in a manner which provides a substantially constant flow of compound to the patient. The following references teach typical sustained release formulations: German Patent 3632201, capsules; Swiss Patent 634990, tablets; German Patent 3237945, buccal tape; German Patent 2732335, tablets; U.S. Patent 5260066, cryogels; European Patent Publication 361894, liposomes; Japanese Patent 84-66710, transdermal patches. Pharmaceutical scientists are acquainted in modern practice with the manners of adjusting a sustained release formulation to provide the desired rate of administration of a given compound and such formulations can be prepared by the skill of the pharmaceutical art of the compounds used as second components here.

Such formulations of the second component compound may be combined in a single dosage form with the chosen first component compound. For example, a small tablet or pellets of the second component, formulated to provide constant availability of the compound, may be combined, for example in a capsule, with the first component compound. Alternatively, a transdermal patch may be prepared which has a relatively rapidly releasing area of first component, and a relatively slowly releasing area of second component. Still further, a suspension may be prepared in which the first component is present as particles of pure compound, and the particles of the second component are coated to provide sustained release in the body. In such manners, the availability of the second component may be adjusted to provide the desired substantially constant blood levels and, hence, substantially constant potentiation of the first component. Compositions so adapted for providing substantially constant potention of the first component are preferred compositions of the present invention.

The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the first component and the second component compound. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations muy be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet hinders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances wich swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as enteric compositions, and even more preferred to formulate them as enteric pellets.

A preferred duloxetine enteric formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. Such a formulation is taught by Anderson, et al, U.S. Patent 5,508,276, incorporated by reference.

Tablets are often coated wih sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Fluoxetine, racemic, hydrochloride	20
WAY 100635	30
Starch, dried	200
Magnesium stearate	10
Total	260 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Fluoxetine, racemic, hydrochloride	10
WAY 100635	40
Cellulose, microcrystaline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	465 mg

The components are blended and compressed to form tablets each weighing 465 mg.

Benefit of the Invention

As stated above, the benefit of the invention is its ability to augment the increase in availability of serotonin caused by the first component compounds, resulting in improved activity in treating the variuos conditions described below in detail. The increase in availability of serotonin is particularly important and is a preferred aspect of the invention. Further, the invention provides a more rapid onset of action than is usually provided by treatment with fluoxetine or duloxetine alone. The experimental data shown below clearly demonstrate the rapid onset of action, as well as the augmentation of availability of the monoamines.

Preferred pathological conditions to be treated by the present method of adjunctive therapy include depression, obsessive-compulsive disease and obesity. Another preferred condition more specific to combinations including preferably duloxetine but also venlafaxine is urinary incontinence.

Depression in its many variations has recently become much more visible to the general public that it has previously been. It is now recognized as an extremely damaging disorder, an one that afflicts a surprisingly large fraction of the population. Suicide is the most extreme symptom of depression, but millions of people, not quite so drastically afflicted, live in misery and partial or complete uselessness, and afflict their families as well by their affliction. The introduction of fluoxetine was a breakthrough in the treatment of depression, and depressives are now much more likely to be diagnosed and treated that they were only a decade ago. Duloxetine is in clinical trials for the treatment of depression and is likely to become a marketed drug for the purpose.

Depression is often associated with other diseases and conditions, or caused by such other conditions. For example, it is associated with Parkinson's disease; with HIV; with Alzheimer's disease; and with abuse of anabolic steroids. Depression may also be associated with abuse of any substance, or may be associated with behavioral problems resulting from or occurring in combination with head injuries, mental retardation or stroke. Depression in all its variations is a preferred target of treatment with the present adjunctive therapy method and compositions.

Obsessive-compulsive disease appears in a great variety of degrees and symptoms, generally linked by the patients's uncontrollable urge to perform needless, ritualistic acts. Acts of acquiring, ordering, cleansing and the like, beyond any rational need or rationale, are the outward characteristic of the disease. A badly afflicted patient may be unable to do anything but carry out the rituals required by the disease. Fluoxetine is approved in the United States and other countries for the treatment of obsessive-compulsive disease and has been found to be effective.

Obesity is a frequent condition in the American population. It has been found that fluoxetine will enable an obese patient to lose weight, with the resulting benefit to the patient's circulation and heart condition, as well as general well being and energy.

Urinary incotinence is classified generally as stress or urge incotinence, depending on whether its root cause is the inability of the sphincter muscles to keep control, or the overactivity of the bladder muscles. Duloxetine controls both types of incontinence, or both types at once, an so is important to the many people who suffer from this embarrassing and disabling disorder.

The present invention is useful for treating many other diseases, disorders and conditions as well, as set out below. In many cases, the diseases to be mentioned here are classified in the International Classification of Diseases, 9th Edition (ICD), or in the Diagnostic and Statistical Manual of Mental Disorders, 3rd Version Revised, published by the American Psychiatric Association (DSM). In such cases, the ICD or DSM code numbers are supplied below for the convenience of the reader.

depression, ICD 296.2 & 296.3, DSM 296, 294.80, 293.81, 293.82, 293.83, 310.10, 318.00, 317.00 migraine

pain, particularly neuropathic pain, bulimia, ICD 307.51, DSM 307.51
premenstrual syndrome or late luteal phase syndrome, DSM 307.90
alcoholism, ICD 305.0, DSM 305.00 & 303.90
tobacco abuse, ICD 305.1, DSM 305.10 & 292.00
panic disorder, ICD 300.01, DSM 300.01 & 300.21
anxiety, ICD 300.02, DSM 300.00
post-traumatic syndrome, DSM 309.89
memory loss, DSM 294.00
dementia of aging, ICD 290
social phobia, ICD 300.23, DSM 300.23
attention deficit hyperactivity disorder, ICD 314.0
disruptive behavior disorders, ICD 312
impulse control disorders, ICD 312, DSM 312.39 & 312.34
borderline personality disorder, ICD 301.83, DSM 301.83
chronic fatigue syndrome
premature ejaculation, DSM 302.75
erectile difficulty, DSM 302.72
anorexia nervosa, ICD 307.1, DSM 307.10
disorders of sleep, ICD 307.4
autism
mutism
trichotillomania

Esperimental Results

A representative combination of the present invention has been tested in conscious experimental animals and the surprising results of the testing demonstrate the benefit of the invention. The tests were carried out as follows.

Microdialysis assays of monoamines

Standard laboratory rats were surgically implanted with microdialysis probes under anesthesia. A stereotaxic instrument was used to implant the probe in the brain. After a recovery period, filtered artificial cerebrospinal fluid was perfused through the probe. At the end of each 20 minute sampling period, dialysate collected in the loop was injected on an analytical column. Dialysate collected in the loop was assayed for 5-HT.

The data has been rounded to make the trends more visible.

Test 1

In this test, the combination therapy comprised fluoxetine as the hydrochloride of the racemate and WAY 100635. The rats were prepared as described above, and the baseline serotonin level was measured for 80 minutes and taken as the 100% level. Fluoxetine was then administered at 10 mg/kg, and WAY 100635 at 1 mg/kg was administered 200 minutes after the start of the experiment.

The 5-HT level measured in the dialysate rose to about the 200% level upon administration of fluoxetine. It increased sharply upon administration of WAY 100635 and was measured at about 550% at 240 minutes, and about 400% of baseline at 300 and 400 minutes.

Claims

1. The pharmaceutical use of a second component which is WAY 100635 for potentiating the action of a first component chosen from the group consisting of fluoxetine, venlafaxine and duloxetine in increasing the availability of serotonin in the brain of a patient.

2. A use of claim 1 wherein the first component is fluoxetine.

3. A use of claim 1 wherein the first component is venlafaxine or duloxetine.

4. A use of claim 1 wherein a pathological condition which is created by or is dependent upon decreased availability of serotonin is treated.

5. A use of claim 4 wherein the first component is fluoxetine.

6. A use of claim 4 wherein the pathological condition is depression.

7. The use for manufacture of a pharmaceutical composition of a first component chosen from the group consisting of fluoxetine, venlafaxine and duloxetine in combination with a second component which is WAY 100635.

8. The use of fluoxetine of claim 7.

9. The use of claim 7 wherein the WAY 100635 is prepared in a manner which provides a substantially constant blood level of it, which level is sufficient to provide a substantially constant degree of potentiation of the action of the first component.

10. The use of claim 9 wherein the first component is fluoxetine.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 96 50 0097

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	EP-A-0 687 472 (ELI LILLY AND COMPANY) * page 2, line 25-32 * * page 5, line 34 - page 6, line 2 * * page 7-8 * * page 13, line 29-37; claims 1-4,6-8,10-12,14,15 * ---	1-10	A61K31/505 //(A61K31/505, 31:135), (A61K31/505, 31:38)
Y	EP-A-0 714 663 (ELI LILLY AND COMPANY) * page 2, line 12-27 * * page 5; claims 1,6,7,10 * * page 11-12 * ---	1-10	
A	BR. J. PHARMACOL., vol. 115, no. 6, 1995, pages 1064-1070, XP000604130 GARTSIDE ET AL: "INTERACTION BETWEEN A SELECTIVE 5-HT1A RECEPTOR ANTAGONIST AND AN SSRI IN VIVO: EFFECTS ON 5-HT CELL FIRING AND EXTRACELLULAR 5-HT" * page 1067, right-hand column - page 1069 * --- -/--	1,4,6	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

A61K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	23 October 1996	Kanbier, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 96 50 0097

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	ARCHIVES OF GENERAL PSYCHIATRY, vol. 51, no. 3, 1994, pages 248-251, XP000605678 ARTIGAS ET AL: "PINDOLOL INDUCES A RAPID IMPROVEMENT OF DEPRESSED PATIENTS TREATED WITH SEROTONIN REUPTAKE INHIBITORS" * page 249, left-hand column * ---	1,2,4-6, 9	
A	J. NEUROCHEM., vol. 66, no. 2, 1996, pages 599-603, XP000604121 ENGLEMAN ET AL: "ANTAGONISM OF SEROTONIN 5-HT1A RECEPTORS POTENTIATES THE INCREASES IN EXTRACELLULAR MONOAMINES INDUCED BY DULOXETINE IN RAT HYPOTHALAMUS" * page 601-602 * ---	1,3,4,6	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	US-A-4 940 585 (W.E. HAPWORTH) * column 2-4; claims 1-3,14,17-19 * -----	1	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

EP 96 50 0097 - C -

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extend that it is not possible to carry out a meaningfull search in the state of the art on the basis of some of the claims.

Claims searched completely:
Claims searched incompletely: 1-6
Claims not searched:

Reason for the limitation of the search: Although claims 1-6 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.